***In the Specification***

Please add the following fourteen new paragraphs (in the order given below) after paragraph [0325] but before paragraph [0326] in the present application. This subject matter is from the inventor's paper (Annals of Human Genetics, 1998, vol. 62, pp. 159-179) which is incorporated into the application by reference. The entire paper is now freely available online without charge in pdf format from the publisher, Blackwell-Synergy, at webaddress http://www.blackwell-synergy.com/loi/ahg .

[0325.01] BACKGROUND INFORMATION FROM THE INVENTOR'S PAPER (ANNALS OF HUMAN GENETICS, 1998, VOL. 62, PP. 159-179).

[0325.02] The following background information is found in the inventor's paper (Annals of Human Genetics, 1998, vol. 62, pp. 159-179). This paper is incorporated into the application by reference and is referred to herein as AHG98. The paper is referred to in the Background in paragraph [0029]. The entire paper is now freely available online in pdf format from the publisher, Blackwell-Synergy, at webaddress http://www.blackwell-synergy.com/loi/ahg . (Issues of the journal over two years old are available free of charge.) The paper compares the transmission/disequilibrium test (TDT) and affected sib pair (ASP) test under a general algebraic model describing a bi-allelic disease locus. Assuming linkage to a bi-allelic marker, two binomial probabilities are derived, one for parental allele 'transmission' *($P_t$)* which determines the magnitude of the TDT $\chi^2$ statistic ($\chi^2_{tdt}$), and a second for identity-by-descent (ibd) marker allele 'sharing' *($P_s$)* which determines the magnitude of the ASP test statistic ($\chi^2_{asp}$). A general framework for determining the power of the TDT and ASP test is presented based on expressions for $P_t$, $P_s$ and the proportion *(H/F)* of ascertained parents who are informative at the marker. The previous analytic investigations of TDT power based on the work of Risch & Merikangas (1996) and others are shown to be a special case of the general framework. (See Abstract AHG 98 p. 159)

[0325.03] The $\chi^2_{tdt}$ statistic for detecting linkage by the TDT is

$\chi^2_{tdt} = (n_a - n_b)^2 / (n_a + n_b) = (n_a - n_b)^2 / n_{tdt}$ where $n_a$ and $n_b$ are the number of instances in which an A/B parent transmitted allele A or B, respectively to an individual affected offspring; and thus $n_a + n_b = n_{tdt}$ is the sample size for $\chi^2_{tdt}$ (see AHG 98 p. 161).

[0325.04] GENERAL ALGEBRAIC MODEL OF LINKAGE (p. 161 and top p.162 of AHG98): The expression for $P_t$, given in the Theory of Operation Section, is based on the following general model: A bi-allelic marker with alleles A and B is linked to a bi-allelic disease locus with disease-predisposing allele D and non-predisposing allele d. The model allows any penetrance for the D/D, D/d and d/d genotypes ($\alpha$, $\beta$, and $\gamma$, respectively) such that $1 \geq \alpha \geq 0$, $1 \geq \beta \geq 0$, and $1 \geq \gamma \geq 0$. The recombination fraction ($\theta$) between marker and disease locus is variable as are the population frequencies of the four marker-disease locus haplotypes [$f(AD) = c_1$, $f(Ad) = c_2$, $f(BD) = c_3$, $f(Bd) = c_4$, where $c_1 + c_2 + c_3 + c_4 = 1$]. Note that once the haplotype frequencies are specified, the population frequency ($p$) of disease allele D is known ($p = c_1 + c_3$) as are the frequencies ($m$, $1-m$) of marker alleles A and B, respectively ($m = c_1 + c_2$, $1 - m = c_3 + c_4$). Furthermore, the coefficient of disequilibrium ($\delta$) equals $c_1c_4 - c_2c_3$ and thus, when convenient, the haplotype frequencies can be expressed as $c_1 = mp + \delta$, $c_2 = m(1-p) - \delta$, $c_3 = (1-m)p - \delta$, $c_4 = (1-m)(1-p) + \delta$. The expression for $P_t$ is given in terms of standard genetic variables for the general bi-allelic model described above. The expression assumes that parents are ascertained through a randomly selected ASP and applies to an ascertained parent who is also heterozygous A/B at a bi-allelic marker. $P_t$ is the probability that the parent transmitted allele A to a particular affected child. ($P_s$ is based on similar assumptions.)

[0325.05] PARAMETERIZATION: The degree of risk conferred by the disease locus can be quantified by considering the penetrance of the D/D homozygote ($\alpha$) to be r times greater than the penetrance of the d/d homozygote ($\gamma$). Thus, $\alpha = r\gamma$ and the penetrance of D/d ($\beta$) can be considered to fall between $\alpha$ and $\gamma$ by letting $\beta = \gamma + x(\alpha - \gamma) = \gamma + x(r-1)\gamma$ where x is a number between 0 and 1. Susceptibility loci causing a modest increase in disease risk are indicated by low values of r. (See p. 163 AHG).

[0325.06] COMPARISON AND CALCULATION OF $\chi^2_{asp}$ AND $\chi^2_{tdt}$ POWER, e.g. when both tests are applied to a bi-allelic marker, (see AHG98 pp. 163 bottom and top 164). It is assumed the two tests evaluate a series of S randomly ascertained parents of one or more ASPs, and that each test considers one ASP per parent. The quantity H/F is the proportion of the S parents who are informative at a bi-allelic marker. The quantity F is proportional to the population frequency of parents who have two or more affected children, and H is proportional to the frequency of such parents who are also heterozygous at the marker. Thus H/F determines the sample size for $\chi^2_{tdt}$. The sample size for $\chi^2_{tdt}$ is $n_{tdt} = 2(H/F)S$. Based on sample size ($n_{asp}$, $n_{tdt}$) and binomial probability ($P_s$, $P_t$), two binomial distributions are generated which can be used to calculate the power of $\chi^2_{asp}$ and $\chi^2_{tdt}$ as described in Appendix II of the paper. Specifically, the power of $\chi^2_{asp}$ or the probability that $\chi^2_{asp} > L$ (a significance cutpoint) is equal to the portion of the binomial distribution based on $P_s$ for which $n_s > n_{asp}/2 + (\sqrt{(n_{asp} L)})/2$. Similarly, if marker allele A is associated with disease, the power of $\chi^2_{tdt}$ is estimated by the portion of the binomial distribution based on $P_t$ (below) for which $n_a > n_{tdt}/2 + (\sqrt{(n_{tdt} L)})/2$. The expression for the binomial distribution based on $P_t$ is:

[0325.07] $$\frac{n_{tdt}!}{n_a! n_b!} P_t^{na} (1-P_t)^{nb}$$

[0325.08] Standard tables giving the normal approximation to the binomial distribution (e.g., (1) Pearson & Hartley (ed) (1954), *Biometrika tables for statisticians*, Vol 1,. Cambridge University Press or (2) Weir, B.S. (ed) (1996) *Genetic data analysis II*, 2nd ed., Sinauer Associates Inc., Sunderland, MA.) give precise power values for virtually any sample size ($n_{asp}$, $n_{tdt}$), binomial probability ($P_s$, $P_t$), and significance level (see AHG 98 p. 164).

[0325.09] The equations for $P_t$, $P_s$ and H/F can be used to compare (and calculate) the power of $\chi^2_{tdt}$ and $\chi^2_{asp}$. The calculations assume that the two tests consider markers that are tightly (closely) linked (recombination fraction $\theta = 0$) to bi-allelic disease loci with additive mode of inheritance ( $\beta = (\alpha + \gamma)/2$ ) and for which the $\alpha$:$\gamma$ penetrance ratio is r = 2, r = 4 or r = 10. Penetrance ratios of r = 2, 4 and 10 were chosen as being somewhat representative of the entire genetic parameter space since the inventor has found that $P_t$ and $P_s$ increase rapidly as r increases from 2 to 6 with smaller, asymptotic increases in $P_t$ and $P_s$ for r > 10. Furthermore, additive mode of inheritance may also be regarded as being somewhat representative since results from other modes of inheritance do not, in general, substantially differ from results presented in the Tables 1, 2 and 3 of AHG98. See bottom p. 164 AHG98.

[0325.10] Tables 1, 2 and 3 (pp. 165 and 167 of AHG98) give TDT power and H/F values for penetrance ratios 2, 4 and 10 respectively. TDT power is for a 2-tailed test with a significance level of 0.05 and sample size of 200 families; $n_{tdt} = 800(H/F)$. Mode of inheritance is additive for all Tables. There is a column in each table for $\delta = 1/2\ \delta_{max}$ and $\delta = \delta_{max}$ and a footnote in each Table describes similar power results for $\delta = 1/2\ \delta_{min}$ and $\delta = \delta_{min}$. Rows in each table give TDT power and H/F values for disease allele frequencies p = 0.60, 0.40 and 0.15; and for each of the disease allele frequencies, p, TDT power and H/F values are given for marker allele frequencies m = 0.75, 0.50, and 0.25 respectively. Calculated TDT power values in the Tables are as low as 0.07 and as high as 0.99. Some observations regarding calculated TDT power and the ability of the TDT to detect linkage are given on page 166.

[0325.11] Tables 1–3 of AHG98 show that when the disease locus and marker are bi-allelic, TDT power is substantially increased if the disease allele and positively associated marker allele have similar frequencies. Muller-Myshok & Abel (1997 Technical Comments Science vol. 275, 1328-1329) independently made a similar observation, but they emphasized the weakness of TDT power when the m/p ratio departs from unity and $\delta$ is not close to $\delta_{max}$. However, the tables illustrate that similar frequencies for the disease allele and associated marker allele can increase TDT power to reasonably high levels even when the m/p ratio substantially differs from 1 and $\delta$ is much lower than $\delta_{max}$. For example, in Table 2 (r = 4), note that when $\delta = 1/2\ \delta_{max}$ and p = 0.15 a similar frequency (m =0.25) for the disease-associated marker allele produces TDT power of 0.86 and $P_t$ of 0.581; but when p = 0.15 and m = 0.5 at $\delta = 1/2\ \delta_{max}$, TDT power and $P_t$ fall to 0.53 and 0.547, respectively. The difference in TDT power for these two situations can also be quantified by calculating the mean value of $\chi^2_{tdt}$ based on a sample of 200 ASP families and the values of $P_t$ and H/F in Table 2 [i.e. $\chi^2_{tdt} = 800(H/F)(2P_t-1)^2$]. When p = 0.15 and m =0.5, $\chi^2_{tdt}$ = 3.53 yielding a significance level of p = 0.06; but when p = 0.15 and m = 0.25, $\chi^2_{tdt}$ = 9.02 for a significance level of p < 0.003. The large difference in significance level (0.06 versus 0.003) and power (0.53 versus 0.86) illustrated by this example indicates that careful attention to allele frequencies at bi-allelic markers may play an important role in future efforts to map susceptibility loci. See AHG98 bottom p. 166 and top p. 168.

[0325.12] The TDT can be applied to families with one affected child. An expression analogous to $P_t$ (denoted $P_t^*$) for families with one affected child and analogous expressions for H (H*) and F (F*) are also given in AHG98. The algebraic form of $P_t^*$ is similar to $P_t$ and the values of $P_t^*$ and $P_t$ are identical for the Risch & Merikangas model and are similar (though not identical) for many other genetic models. See AHG 98 top DISCUSSION top p. 168 and top and mid p. 169. The framework given in the paper generalizes the analysis of Risch & Merikangas by encompassing many modes of inheritance rather than just one and enabling TDT power to be calculated for a marker that is distinct from the disease locus (e.g., $m \neq p$), see AHG98 bottom of p. 170 and top and 171.

$$P_t^* = 0.5 + (1-2\theta)[(c_1c_4 - c_2c_3)/H^*]\{p^2(\alpha-\beta)/2 + p(1-p)(\alpha-\gamma)/2 + (1-p)^2(\beta-\gamma)/2\}$$

$$H^* = 2(c_1c_4 + c_2c_3)\,[(p\alpha - p\gamma+\beta+\gamma)/2] + 2c_1c_3\{\,p\alpha - p\beta + \beta\}$$

$$+ 2\,c_2c_4\{\,p\beta - p\gamma+\gamma\}$$

$$F^* = p^2\alpha + 2p(1-p)\beta + (1-p)^2\gamma$$

[0325.13] Expression for F, see p. 169 of AHG98.

$$F = p^4\alpha^2 + 4p^3(1-p)[(\alpha+\beta)/2]^2 + 2p^2(1-p)^2\beta^2 + 4p^2(1-p)^2[(\alpha+2\beta+\gamma)/4]^2$$
$$+ 4p(1-p)^3[(\beta+\gamma)/2]^2 + (1-p)^4\gamma^2$$

[0325.14] Expression for H, see p. 174 of AHG98.

$$H = 2(c_1c_4 + c_2c_3)\{p^2[(\alpha+\beta)/2]^2 + (1/2)p(1-p)[(\alpha+2\beta+\gamma)/2]^2 + (1-p)^2[(\beta+\gamma)/2]^2\}$$
$$+2\,c_1c_3\{p^2\alpha^2 + (1/2)p(1-p)(\alpha+\beta)^2 + (1-p)^2\beta^2\}$$
$$+\,2\,c_2c_4\{p^2\beta^2 + (1/2)p(1-p)(\beta+\gamma)^2 + (1-p)^2\gamma^2\}$$